

WHAT IS CLAIMED IS:

1. An adenovirus fiber comprising a binding site for a cellular receptor, the adenovirus fiber comprising a mutation of a residue of the fiber characterized in that the residue is directed to the binding site for a blood factor protein, wherein the mutation reduces the affinity of the fiber for the blood factor protein.
- 5 2. The adenovirus fiber according to claim 1, wherein the blood factor protein is Factor IX, TFPI, C3-precursor, complement C4, complement C4BP, hemopexin, fibrinogen, elastase-1 or pregnancy zone protein.
3. The adenovirus fiber according to claim 1, characterized in that the mutation is in the fiber knob.
- 10 4. The adenovirus fiber according to claim 3, characterized in that the mutation is in the AB, FG or HI loop.
5. The adenovirus fiber according to claim 1, wherein the adenovirus fiber comprises a short shaft.
- 15 6. The adenovirus fiber according to claim 1, characterized in that the mutation is in a loop in the fiber knob, wherein the affinity of the fiber knob for the native cellular receptor is not substantially reduced.
7. The adenovirus fiber according to claim 6, characterized in that the fiber knob is derived from a type 5 adenovirus (Ad5) fiber knob.
- 20 8. The Ad5 adenovirus fiber according to claim 7, characterized in that it is modified by mutation of a residue in the AB, EF or HI exposed loop.
9. The adenovirus fiber according to claim 6, characterized in that it is derived from a group B type 35 adenovirus (Ad5) fiber knob.
10. The Ad35 adenovirus fiber according to claim 9, characterized in that it is modified by mutation of a residue in the AB, EF or HI exposed loop.
- 25 11. The adenovirus fiber according to claim 6, characterized in that it is derived and Ad2 fiber.

12. The adenovirus fiber according to claim 11, characterized in that it is modified by mutation of a residue in the AB, EF or HI exposed loop.

13. The adenovirus fiber according to claim 1, wherein the binding affinity of the fiber for its native cellular receptor is not substantially reduced.

5 14. The adenovirus fiber of claim 1, wherein binding to the blood factor protein is ablated.

15. The adenovirus fiber according to claim 1, comprising a ligand capable of recognizing a cell surface molecule different from the native cellular receptor for adenovirus fiber.

10 16. The adenovirus fiber according to claim 15, characterized in that the ligand is an antibody, a peptide, a lipid, a glycolipid, or a sugar.

17. The adenovirus fiber according to claim 15, characterized in that the ligand is inserted at the C-terminal end of the fiber, in the HI loop, in capsid protein IX, in the penton or in the hexon.

15 18. A DNA fragment or expression vector encoding the adenovirus fiber according to claim 1.

19. A cell line comprising the DNA fragment of claim 18 in a form integrated into the genome or in the form of an episome, wherein the DNA fragment is operatively linked to a promoter for expression of the adenovirus fiber in the cell line.

20 20. The cell line according to claim 19, further comprising a function encoded by the E1, E2, E4 or L1-L5 region and capable of complementing an adenovirus deficient in a function encoded by the E1, E2, E4 or L1-L5 region.

21. The cell line according to claim 19, characterized in that it is derived from a 293 cell line.

25 22. An adenovirus comprising the adenovirus fiber according to claim 1.

23. An adenovirus characterized in that it lacks a functional native fiber and in that it comprises a fiber according to claim 1 and a ligand capable of recognizing a cell surface molecule different from the native cellular receptor for the adenovirus.

24. The adenovirus according to claim 23, characterized in that the ligand is an antibody, a peptide, a lipid, a polypeptide, a glycolipid or a sugar.

25. The adenovirus according to claim 23, characterized in that the ligand is inserted at the C-terminal end of the fiber, in the HI loop, in capsid protein IX, in the penton or in the hexon.

26. The adenovirus according to claim 23, characterized in that the ligand is inserted into an adenovirus capsid protein.

27. The adenovirus according to claim 26, characterized in that the ligand is inserted into the hexon, the penton or the fiber.

28. The adenovirus according to claim 22, characterized in that it is a replication-defective or replication-attenuated recombinant adenovirus.

29. The adenovirus according to claim 28, characterized in that it is deleted for all or part of the E1 region and, optionally, for all or part of the E3 region.

30. The adenovirus according to claim 29, characterized in that it is further deleted for all or part of the E2, E4 or L1-L5 region.

31. The adenovirus according to claim 29, characterized in that it comprises a gene of interest selected from a cytokine, a cellular receptor, a nuclear receptor, a ligand, a coagulation factor, a CFTR protein, insulin, dystrophin, a growth hormone, an enzyme, an enzyme inhibitor, a polypeptide with antitumor effect, a polypeptide capable of inhibiting a bacterial, parasitic or viral infection, an antibody, a toxin, an immunotoxin or a marker.

32. A method of producing an adenovirus according to claim 22, comprising:

transfecting a genome encoding the adenovirus into a host cell line,

culturing the transfected host cell line under appropriate conditions to allow the production of the adenovirus,
recovering the adenovirus from the culture of the transfected host cell line, and optionally substantially purifying the adenovirus.

5 33. A host cell infected with an adenovirus according to claim 22.

 34. A pharmaceutical composition comprising an adenovirus according to claim 22 in combination with a pharmaceutically acceptable carrier.

 35. The pharmaceutical of claim 34, wherein the adenovirus is a replication-defective or replication-attenuated recombinant adenovirus.

10 36. The adenovirus of claim 35, characterized in that it comprises a gene of interest selected from a cytokine, a cellular receptor, a nuclear receptor, a ligand, a coagulation factor, a CFTR protein, insulin, dystrophin, a growth hormone, an enzyme, an enzyme inhibitor, a polypeptide with antitumor effect, a polypeptide capable of inhibiting a bacterial, parasitic or viral infection, an antibody, a toxin, an immunotoxin or a marker.

15 37. A pharmaceutical composition comprising an infected host cell according to claim 33 in combination with a pharmaceutically acceptable carrier.

 38. The pharmaceutical of claim 37, wherein the adenovirus is a replication-defective or replication-attenuated recombinant adenovirus.

20 39. The pharmaceutical of claim 38, characterized in that it comprises a gene of interest selected from a cytokine, a cellular receptor, a nuclear receptor, a ligand, a coagulation factor, a CFTR protein, insulin, dystrophin, a growth hormone, an enzyme, an enzyme inhibitor, a polypeptide with antitumor effect, a polypeptide capable of inhibiting a bacterial, parasitic or viral infection, an antibody, a toxin, an immunotoxin or a marker.

25 40. The therapeutic or prophylactic use of an adenovirus according to claim 22, for the preparation of a medicament intended for the treatment of the human or animal body by gene therapy.

 41. A method for increasing the efficacy of adenoviral vector administration, comprising:

administering to a subject a recombinant adenovirus vector comprising a gene of interest and encoding a mutant adenoviral fiber comprising a binding site for a cellular receptor and a mutated blood factor protein binding site, wherein the affinity of the fiber for the blood factor protein is substantially reduced.

5 42. The method according to claim 41, wherein the cellular receptor is a native cellular receptor.

 43. The method according to claim 41, wherein the binding site for the cellular receptor is a ligand.

10 44. The method according to claim 43, wherein the ligand is an antibody, a peptide, a hormone, a polypeptide or a sugar.

 45. The method according to claim 41, wherein the gene of interest is a cytokine, a cellular receptor, a nuclear receptor, a ligand, a coagulation factor, a CFTR protein, insulin, dystrophin, a growth hormone, an enzyme, an enzyme inhibitor, a polypeptide with antitumor effect, a polypeptide capable of inhibiting a bacterial, parasitic or viral infection, an antibody, a toxin, an immunotoxin or a marker.

 46. The method according to claim 41, wherein the gene of interest is operatively linked to a promoter.

 47. The method according to claim 46, wherein the promoter is a tissue-specific promoter.

20 48. A method for reducing toxicity associated with adenovirus administration, comprising:

 administering to a subject a recombinant adenovirus or adenoviral vector comprising a gene of interest and a mutant adenoviral fiber comprising a binding site for a cellular receptor and a mutated blood factor protein binding site, wherein the affinity of the fiber for the blood factor protein is substantially reduced.

25 49. The method according to claim 48, wherein the cellular receptor is a native cellular receptor.

50. The method according to claim 48, wherein the binding site for the cellular receptor is a ligand.

51. The method according to claim 50, wherein the ligand is an antibody, a peptide, a hormone, a polypeptide or a sugar.

5 52. The method according to 48, wherein the gene of interest is a cytokine, a cellular receptor, a nuclear receptor, a ligand, a coagulation factor, a CFTR protein, insulin, dystrophin, a growth hormone, an enzyme, an enzyme inhibitor, a polypeptide with antitumor effect, a polypeptide capable of inhibiting a bacterial, parasitic or viral infection, an antibody, a toxin, an immunotoxin or a marker.